PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P015404Wo CYK	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/SG2004/000098	International filing date *(day/month/year)* 16.04.2004	Priority date *(day/month/year)* 17.04.2003
International Patent Classification (IPC) or national classification and IPC C07K14/47, C12N15/29, A61K39/12, A61K39/35		
Applicant NATIONAL UNIVERSITY OF SYNGAPORE et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.07.2005	10.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Grosskopf, R Telephone No. +49 89 2399-8714

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SG2004/000098

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-215 as originally filed

Sequence listings part of the description, Pages

1-622 as originally filed

Claims, Numbers

1-51 received on 01.08.2005 with letter of 29.07.2005

Drawings, Sheets

1/57-57/57 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 3-27 (all partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 3-27 (all partially) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SG2004/000098

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-27 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-27
	No:	Claims	1,2
Inventive step (IS)	Yes:	Claims	3-27
	No:	Claims	3-27
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Ad item IV:

This Authority agrees completely with the objections for lack of unity raised by the search authority and is also in agreement about the division into the groups which has been made.
In reply to the first search report, the Applicant paid three additional fees and requested a search for claims 1-48, 54-59, 63-67 and 77-78 which, in the opinion of the Applicant, merely constitute four groups of inventions.
Although the search authority maintained its objections, in agreement with the Applicant, nevertheless declared its readiness to carry out the search for the claims as requested by the Applicant.
This occurred after having made a balance between the amount of fees which had to be paid for the Applicant and the work which had to be carried out by the search authority.
Unfortunately also the amended set of claims filed with the letter of 29.07.05 lacked unity and contained at least three alleged inventions (see sheet 405). Consequently the Applicant was invited to pay two additional examination fees, but failed to do so.
Thus, the examination is carried out on the basis of the first group of claims, i.e. Claims 1-27.

Ad item V:

1. The Fve polypeptide is known from D1 and D2 (D1: KO JIUNN-LIANG ET AL: "A new fungal immunomodulatory protein, FIP-fve isolated from the edible mushroom, Flammulina velutipes and its complete amino acid sequence" EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 228, no. 2, 1995, pages 244-249, XP008036978 ISSN: 0014-2956;D2:KO JIUNN-LIANG ET AL: "Molecular cloning and expression of a fungal immunomodulatory protein, FIP-fve, from Flammulina velutipes" JOURNAL OF THE FORMOSAN MEDICAL ASSOCIATION, vol. 96, no. 7, 1997, pages 517-524, XP008036979 ISSN: 0929-6646).
Moreover fusion protein with GST have been described in D1 and D2 (which might be regarded in the broadest interpretation as a (fragment of) an "allergen").
Therefore, claims 1 and 2 lack novelty.

Moreover, when considering that the preparation of fusion proteins of an immune modulator with another protein in general (see D3, US 5917026), including specifically "disease associated antigens", "tumour associated antigens", or viral antigens" (see D4, WO 99/06544; see claims or D5; WO 98/32866), are well known in the art, an inventive activity for the general polypeptides which possibly should form the "unifying concept" of the remaining Claims has to be denied.

As a consequence, the various alternatives of Claims 3 to 12, on the one hand, no longer share a common inventive concept and, thus, give rise to further objections for lack of unity (see also search report).
On the other hand, in view of the fact that the general fusion proteins lack an inventive activity, such an activity for **any** of said specific constructs could only be acknowledged if said construct had some kind of unexpected or surprising property,

Anyhow, in view of the uncountable number of alternatives which are encompassed by the claims (considering that "preferably" does not constitute a limitation of the scope of the claims) a complete or meaningful examination is not possible, neither under the aspect of unity nor under the aspect of clarity.

CLAIMS

1. A polypeptide capable of modulating an immune response against a molecule, the polypeptide comprising:

(a) a first portion being an Fve polypeptide (SEQ ID NO: 6), a fragment thereof comprising at least 20 amino acids or a polypeptide having at least 70% sequence identity thereto, which polypeptide or fragment comprises immunomodulatory activity; and

(b) a second portion being a molecule against which the modulation of the immune response is desired.

2. A polypeptide according to Claim 1, in which the second portion comprises an allergen or a fragment thereof.

3. A polypeptide according to Claim 2, in which the allergen comprises an allergen from a mite, preferably from Family *Glycyphagidae* or Family *Pyroglyphidae*, preferably a group 1 allergen (Der p 1, Der f 1, Blo t 1, Eur m1, Lep d 1), a group 2 allergen (Der p 2, Der f 2, Blo t 2, Eur m 2, Lep d 2), a group 5 allergen (Blo t 5, Der p 5, Der f 5, Eur m 5, Lep d 5) a group 15 allergen (Der p 15, Der f 15, Blot 15, Eur m 15, Lep d 15).

4. A polypeptide according to Claim 2 or 3, which polypeptide is selected from the group consisting of: Blo t 5-Fve (SEQ ID NO: 38), Blo t 5-FveR27A (SEQ ID NO: 40), Blo t 5-FveT29A (SEQ ID NO: 42), Der p 2-Fve, Der p 2-FveR27A (SEQ ID NO: 44), Der p 2-FveT29A (SEQ ID NO: 46), GST-Der p 2-FveR27A, GST-Der p 2-FveT29A, Blo t 5-Der p 2-FveR27A (SEQ ID NO: 48) and Blo t 5-Der p 2-FveT29A.

5. A polypeptide according to Claim 2, in which the allergen is selected from the group consisting of: tree pollen allergen, Bet v 1 and Bet v 2 from birch tree; grass pollen allergen, Phl p 1 and Phl p 2 from timothy grass; weed pollen allergen, antigen E from ragweed; major feline antigen, Fel d; major fungal allergen, Asp f1, Asp f2, and Asp f3 from *Aspergillus fumigatus*.

6. A polypeptide according to Claim 1, in which the second portion comprises a viral antigen or a fragment thereof, the viral antigen preferably being selected from the group consisting of: E6 and E7 from HPV; core Ag and E2 from HCV; core and surface antigens from HBV; LMP-1, LMP-2, EBNA-2, EBNA-3 from EBV; Tax from HTLV-1 and antigens from Adenovirus, Parainfluenza 3 virus, Human Immunodeficiency Virus (HIV-

1, HIV-2), Herpes simplex virus (HSV), Respiratory syncytial virus (RSV), Influenza A virus, Flu A, coronavirus and flavivirus.

7. A polypeptide according to Claim 6 which comprises HPV E7-FveT29A (SEQ ID NO: 49) or HCV Core23-FveT29A (SEQ ID NO: 51).

8. A polypeptide according to Claim 1, in which the second portion comprises a tumour-associated antigen or a fragment thereof, the tumour-associated antigen preferably being selected from the group consisting of: MAGE-1, MAGE-2, MAGE-3, preferably a sequence, BAGE, GAGE, PRAME, SSX-2, Tyrosinase, MART-1, NY-ESO-1, gp100, TRP-1, TRP-2, A2 melanotope, BCR/ABL, Proteinase-3/Myeloblastin, HER2/neu, CEA, P1A, HK2, PAPA, PSA, PSCA, PSMA, pg75, MUM-1, MUC-1, BTA, GnT-V, β-catenin, CDK4, and P15.

9. A polypeptide according to Claim 8 which comprises MAGE3-FveT29A (SEQ ID NO: 53), MART1-FveT29A (SEQ ID NO: 55) or CEA-FveT29A (SEQ ID NO: 57).

10. A polypeptide according to any preceding claim, in which the first portion comprises between 2 to 20 residues of amino acid sequence flanking the glycine residue corresponding to position 28 of Fve.

11. A polypeptide according to any preceding claim, in which the first portion comprises the sequence RGT or the sequence RGD.

12. A polypeptide according to Claim 11 comprising an sequence selected from the group consisting of: Fve R27A (SEQ ID NO: 32), Fve T29A (SEQ ID NO: 36), GST-Fve R27A and GST-Fve T29A.

13. A nucleic acid encoding a polypeptide according to any preceding claim.

14. A nucleic acid according to Claim 13, in which the nucleic acid comprises CGT GGT ACC, or a sequence which differs from the above by virtue of the degeneracy of the genetic code and which encodes a sequence RGT.

15. A nucleic acid according to Claim 13 or 14, which comprises (a) Blo t 5-Fve (SEQ ID NO: 37), Blo t 5-FveR27A (SEQ ID NO: 39), Blo t 5-FveT29A (SEQ ID NO: 41), Der p 2-Fve, Der p 2-FveR27A (SEQ ID NO: 43), Der p 2-FveT29A (SEQ ID NO: 45), GST-Der p 2-FveR27A, GST-Der p 2-FveT29A, Blo t 5-Der p 2-FveR27A (SEQ ID NO: 47) or Blo t 5-Der p 2-FveT29A; (b) HPV E7-FveT29A (SEQ ID NO: 50) or HCV Core23-FveT29A (SEQ ID NO: 52); (c) MAGE3-FveT29A (SEQ ID NO: 54), MART1-FveT29A

(SEQ ID NO: 56) or CEA-FveT29A (SEQ ID NO: 58); or (d) Fve R27A (SEQ ID NO: 31), Fve T29A (SEQ ID NO: 35), GST-Fve R27A or GST-Fve T29A.

16. A vector, preferably an expression vector, comprising a nucleic acid sequence according to any of Claims 13 to 15.

17. A DNA vaccine, a host cell or a transgenic non-human organism, preferably a bacterium, a yeast, a fungus, a plant or an animal, more preferably a mouse, comprising a nucleic acid according to any of Claims 13 to 15 or a vector according to Claim 16.

18. A pharmaceutical composition comprising a polypeptide according to any of Claims 1 to 12, a nucleic acid according to any of Claims 13 to 15, a vector according to Claim 16, or a DNA vaccine or a host cell according to Claim 17, together with a pharmaceutically acceptable carrier or diluent.

19. A polypeptide, nucleic acid, vector, DNA vaccine, host cell or a pharmaceutical composition according to any of Claims 1 to 18 for use in the treatment of a disease.

20. Use of a polypeptide, nucleic acid, vector, DNA vaccine, host cell or a pharmaceutical composition according to any of Claims 1 to 18 for the preparation of a pharmaceutical composition for the treatment of a disease.

21. Use of a polypeptide, nucleic acid, vector, DNA vaccine, host cell or a pharmaceutical composition according to any of Claims 1 to 18 as an immumodulator, to enhance an immune response in a mammal, or as an adjuvant for a vaccine or in a method of treatment or prophylaxis of a disease.

22. A method of treating an individual suffering from a disease or preventing the occurrence of a disease in an individual, the method comprising administering to the individual a therapeutically or prophylactically effective amount of a polypeptide, nucleic acid, vector, DNA vaccine, host cell or a pharmaceutical composition according to any of Claims 1 to 18.

23. A use or method according to any of Claims 20 to 22, in which the disease comprises an atopic disease or allergy.

24. A use or method according to Claim 23, in which the allergy is selected from the group consisting of: allergic asthma, a seasonal respiratory allergy, a perennial respiratory allergy, allergic rhinitis, hayfever, nonallergic rhinitis, vasomotor rhinitis, irritant rhinitis,

an allergy against grass pollen, weed pollen, tree pollen or animal danders, an allergy associated with allergic asthma and a food allergy.

25. A use or method according to Claim 23 or 24, in which the allergy is to a house dust mite from Family Glyphagidae, preferably *Blomia tropicalis* or from Family Pyroglyphidae, preferably *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*, or to fungi or fungal spores, preferably *Aspergillus fumigatus*, or to tree pollen allergens, preferably from birch tree, or grass pollen allergens, preferably from timothy grass, or weed allergens, preferably ragweed.

26. A use or method according to any of Claims 20 to 22, in which the disease comprises a cancer, preferably by suppressing tumour progression.

27. A use or method according to Claim 26, in which the cancer comprises a T cell lymphoma, leukaemia, brain neoplasms, bladder cancer, renal cancer, hepatoma, melanoma, lung cancer, colon cancer, breast cancer or prostate cancer.

28. Use of a polypeptide comprising an Fve sequence, a fragment thereof or a polypeptide having at least 70% sequence identity thereto, which polypeptide or fragment comprises immunomodulatory activity, a nucleic acid encoding such or a polypeptide according to any of Claims 1 to 12 in a method of stimulating proliferation of $CD3^+$ $CD8^+$ $CD18^{+\,bright}$ T cells.

29. Use of a polypeptide according to any of Claims 1 to 12, an Fve polypeptide, a fragment thereof or a polypeptide having at least 70% sequence identity thereto, which polypeptide or fragment comprises immunomodulatory activity, or a nucleic acid encoding any of the above, in a method of enriching natural killer (NK) T cells in a cell population, or enhancing cytolytic activity of $CD16^+$ $CD56^+$ natural killer (NK) T cells.

30. Use of a polypeptide according to any of Claims 1 to 12, an Fve polypeptide, a fragment thereof or a polypeptide having at least 70% sequence identity thereto, which polypeptide or fragment comprises immunomodulatory activity, or a nucleic acid encoding any of the above, in a method of stimulating production of IL-10 in $CD3^+$ cells.

31. Use according to Claim 30, in which production of IL-4 and IL-13 are not stimulated in the $CD3^+$ cells.

32. A method of amplifying a sub-population of cells, the method comprising: (a) obtaining a population of cells from an individual; (b) amplifying $CD3^+$ $CD8^+$ and $CD18^{+\,bright}$ T cells by exposing the population of cells to a polypeptide according to any of

Claims 1 to 12, an Fve polypeptide, a fragment thereof or a polypeptide having at least 70% sequence identity thereto, which polypeptide or fragment comprises immunomodulatory activity, or a nucleic acid encoding any of the above.

33. A method according to Claim 32, further comprising the step of: (c) isolating the $CD3^+$ $CD8^+$ and $CD18^{+\,bright}$ T cells.

34. A method of treating an individual suffering from a disease or preventing the occurrence of a disease in an individual, the method comprising amplifying a $CD3^+$ $CD8^+$ and $CD18^{+\,bright}$ T cell by a method according to Claim 32 or 33, and administering the amplified $CD3^+$ $CD8^+$ and $CD18^{+\,bright}$ T cell to an individual.

35. A variant Fve polypeptide comprising a Fve polypeptide having a sequence set out in SEQ ID NO: 6 together with a mutation at position 27 of that sequence, or a mutation at position 29 of that sequence, or both.

36. A variant Fve polypeptide according to Claim 35, in which the mutation or mutations independently comprise a substitution to a neutral residue such as glycine (G) or alanine (A).

37. A variant Fve polypeptide according to Claim 35 or 36, in which a mutation at position 27 comprises R27A.

38. A variant Fve polypeptide according to Claim 35, 36 or 37, in which a mutation at position 29 comprises T29A.

39. A variant Fve polypeptide according to any of Claims 35 to 38, comprising mutations at both position 27 and position 29, preferably R27A and T29A.

40. A variant Fve polypeptide according to any of Claims 35 to 39, comprising an sequence selected from the group consisting of: Fve R27A (SEQ ID NO: 32), Fve T29A (SEQ ID NO: 36), GST-Fve R27A, and GST-Fve T29A.

41. A variant Fve polypeptide according to any of Claims 35 to 40, which has an increased activity as compared to the wild type Fve polypeptide (SEQ ID NO: 6) selected from the group consisting of: up-regulation of expression of Th1 cytokines, preferably IFN-γ and TNF-α, down-regulation of expression of Th2 cytokines, preferably IL-4 and IL-13, hemagglutination activity, cell aggregation activity, lymphocyte aggregation activity, lymphoproliferation activity, up-regulation of expression of IL-2, IFN-γ, TNF-α, but not IL-4 in $CD3^+$ T cells, interaction with T and NK cells, adjuvant activity,

stimulation of $CD3^+$ $CD16^+$ $CD56^+$ natural killer (NK) T cells, and up-regulation of expression of allergen specific IgG2a antibody.

42. A variant Fve polypeptide according to any of Claims 35 to 41, which has an increased solubility compared to the wild type Fve polypeptide (SEQ ID NO: 6).

43. A variant Fve polypeptide which is derivable from a parent polypeptide having the sequence SEQ ID NO: 6, in which the variant Fve polypeptide comprises an amino acid mutation at position 27, or an amino acid mutation at position 29, or both, with reference to the position numbering of SEQ ID NO: 6.

44. A fragment of a variant Fve polypeptide according to any of Claims 35 to 43, which comprises at least 20 residues of amino acid sequence flanking the glycine residue at position 28 of Fve, with reference to the position numbering of SEQ ID NO: 6, which fragment has increased solubility when compared to wild type Fve (SEQ ID NO: 6).

45. A nucleic acid capable of encoding a variant Fve polypeptide according to any of Claims 35 to 44.

46. A nucleic acid according to Claim 45, which is selected from the group consisting of: Fve R27A (SEQ ID NO: 31), Fve T29A (SEQ ID NO: 35), GST-Fve R27A and GST-Fve T29A.

47. A vector, preferably an expression vector, comprising a nucleic acid sequence according to Claim 45 or 46.

48. A DNA vaccine, a host cell or a transgenic non-human organism, preferably a bacterium, a yeast, a fungus, a plant or an animal, more preferably a mouse, comprising a nucleic acid according to Claim 45 or 46 or a vector according to Claim 47.

49. A pharmaceutical composition comprising a variant Fve polypeptide according to any of Claims 35 to 44, a nucleic acid according to any of Claims 45 to 46, a vector according to Claim 47, or a DNA vaccine or a host cell according to Claim 48, together with a pharmaceutically acceptable carrier or diluent.

50. A polypeptide, nucleic acid, vector, DNA vaccine, host cell or a pharmaceutical composition according to any of Claims 35 to 49 for use in the treatment of a disease.

51. Use of a polypeptide, nucleic acid, vector, DNA vaccine, host cell or a pharmaceutical composition according to any of Claims 35 to 49 for a purpose as set out in any of Claims 20 to 34.